Ethics and Complementary and Alternative Medicine (CAM) Research:

Challenges in Risk/Benefit Determination

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Disclaimer

The views presented are those of the author and do not necessarily reflect the position or policies of the National Institutes of Health or the Department of Health and Human Services.

Objectives

1. Review the ethical rationale for studying CAM
2. Review the components of risk-benefit determination
3. Examine several challenges to risk-benefit determination in CAM research

Key Points

1. Favorable Risk/Benefit ratio is essential.
2. Risk/Benefit determination may be more complicated in some CAM research.
3. Difficulties in Risk/Benefit determination involve scientific uncertainty & cultural factors.
4. Practical accommodations may be necessary to implement a fair risk/benefit determination for trials of CAM therapies.

Distinguished Lectures
in the Science of
Complementary and Alternative Medicine

Natural Products: Challenges and Opportunities

Ram Sasisekharan, Ph.D.
Professor of Biological Engineering
Massachusetts Institute of Technology

October 25, 2006 at 11 a.m.
Masur Auditorium, Building 10, NIH

Case

- Large multicenter Hep C trial in Southeast Asia, funded by NIH.
- Herbal medicine*, cyanthus holensus*, or *Asia Flower*, is a popular natural product in the country.
- Many local traditional herbalists believe that *Asia Flower* is effective as complementary or alternative anti-viral therapy.
- The product is already widely utilized within the region for "immune boosting"

Case, continued.

- In vitro, pharmacokinetic studies suggest potential interference with vaccines.
- Animal models show liver toxicity at very high doses.
- There are no systemic side effects reported for humans in the literature.
- There have been a few non-randomized studies of *Asia Flower* with mixed efficacy results.
- Non-NIH collaborators working with regional leaders want the NIH to conduct a large, randomized controlled trial of *Asia Flower* adjunctive treatment for refractory Hep C to assess it's impact on disease progression.

Should the NIH conduct the study?

Is it ethical to conduct this research?

CAM Research: *Ethical Reasons*

- Identifying new therapeutics - Beneficence
- Characterizing safety of treatments already in wide-spread use – Nonmaleficence
- Inform decisions about resource expenditure - Justice

The 8 Criteria – *How Do They Apply?*

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair Subject Selection
5. *Favorable Risk-Benefit Ratio*
6. Independent Review
7. Informed Consent
8. Respect for Subjects

Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA.* 2000;283(20):2701-11.

Favorable Risk-Benefit Ratio

1. Identify and minimized risks
2. Identify and maximize benefits
3. If potential benefits to the individual outweigh risks to the individual then research may proceed.
4. If risks outweigh benefits to the individual, then individual risks must be weighed against social benefit of knowledge gained.

. . . More than "Just the Facts"

Favorable Risk-Benefit Ratio: Vocabulary Questions

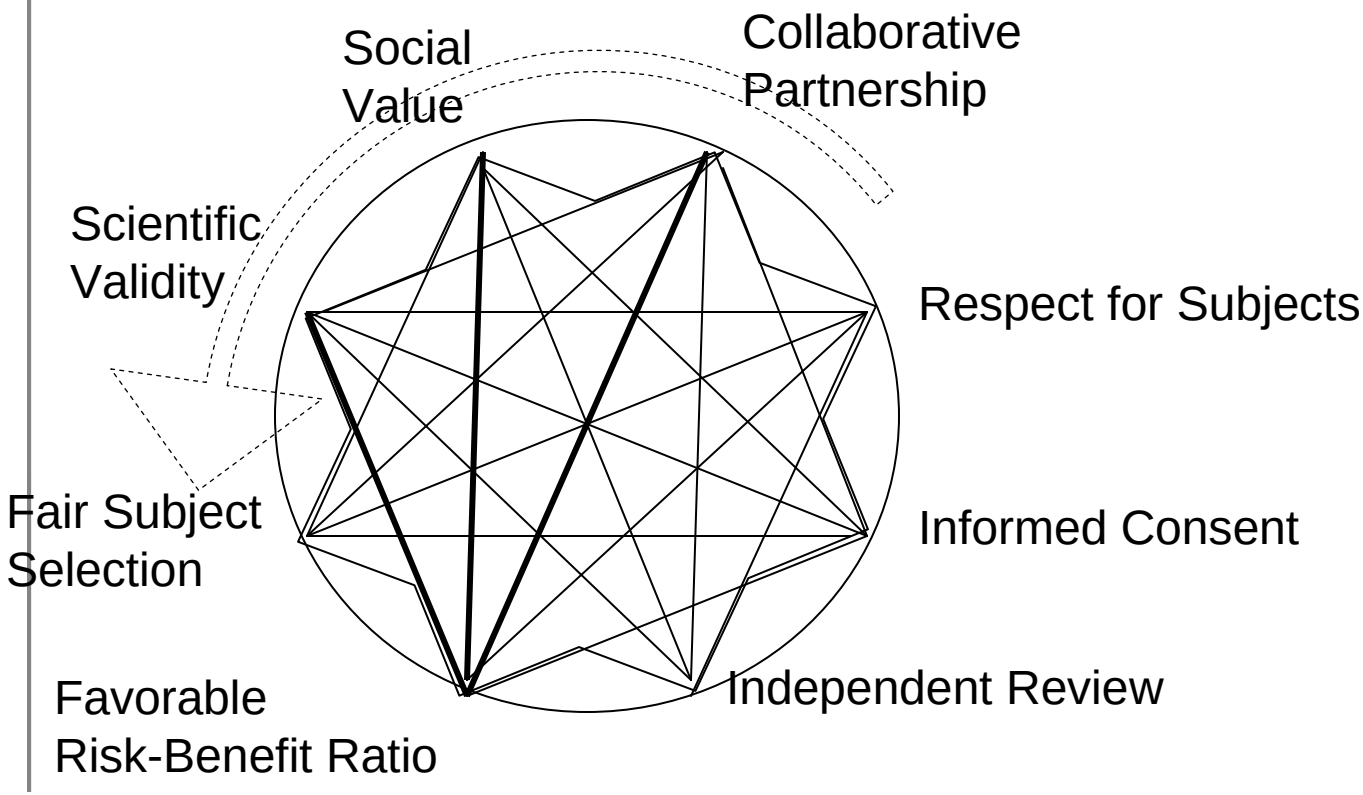
1. What is the metric of risks/benefits?
2. Who or what is the unit of analysis?
3. What goes into "weighing"?
4. Who does the "weighing"?
5. What makes a ratio "favorable"?

Risk-Benefit Determination in CAM Research: Challenges

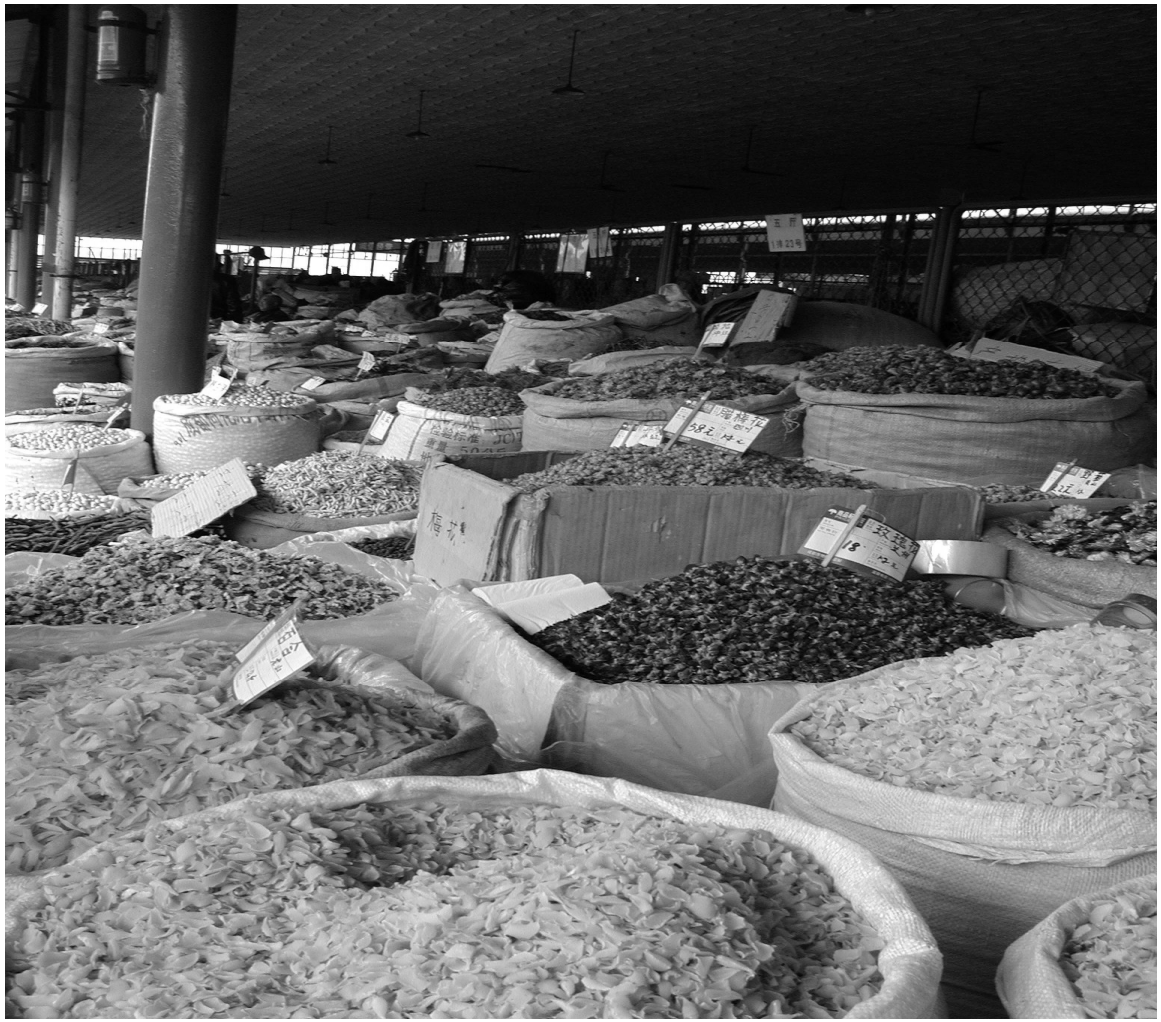
1. Uncertainty in Scientific Validity
2. Cultural Differences

- Collaborative Partnership
- Social Value

8 Ethical Requirements



International Collaborative Herbal Medicine Trials



Practical Differences

Herbal Medicines

- Already in use
- Act synergistically to stimulated harmony and balance
- Different regulatory status

Pharmacotherapeutics

- Formal Approval
- Act by a primary causal mechanism
- Strict regulatory status

What ethical difference (if any) do these differences make ?

Scientific Validity in CAM Research

1. What is the best research design (Miller)
   - Appropriateness of RCTs
   - Appropriateness of placebos
2. Uncertainty related to the current science
3. Inclusion and exclusion criteria
4. Appropriate outcome measures

Scientific Validity: The Current Science

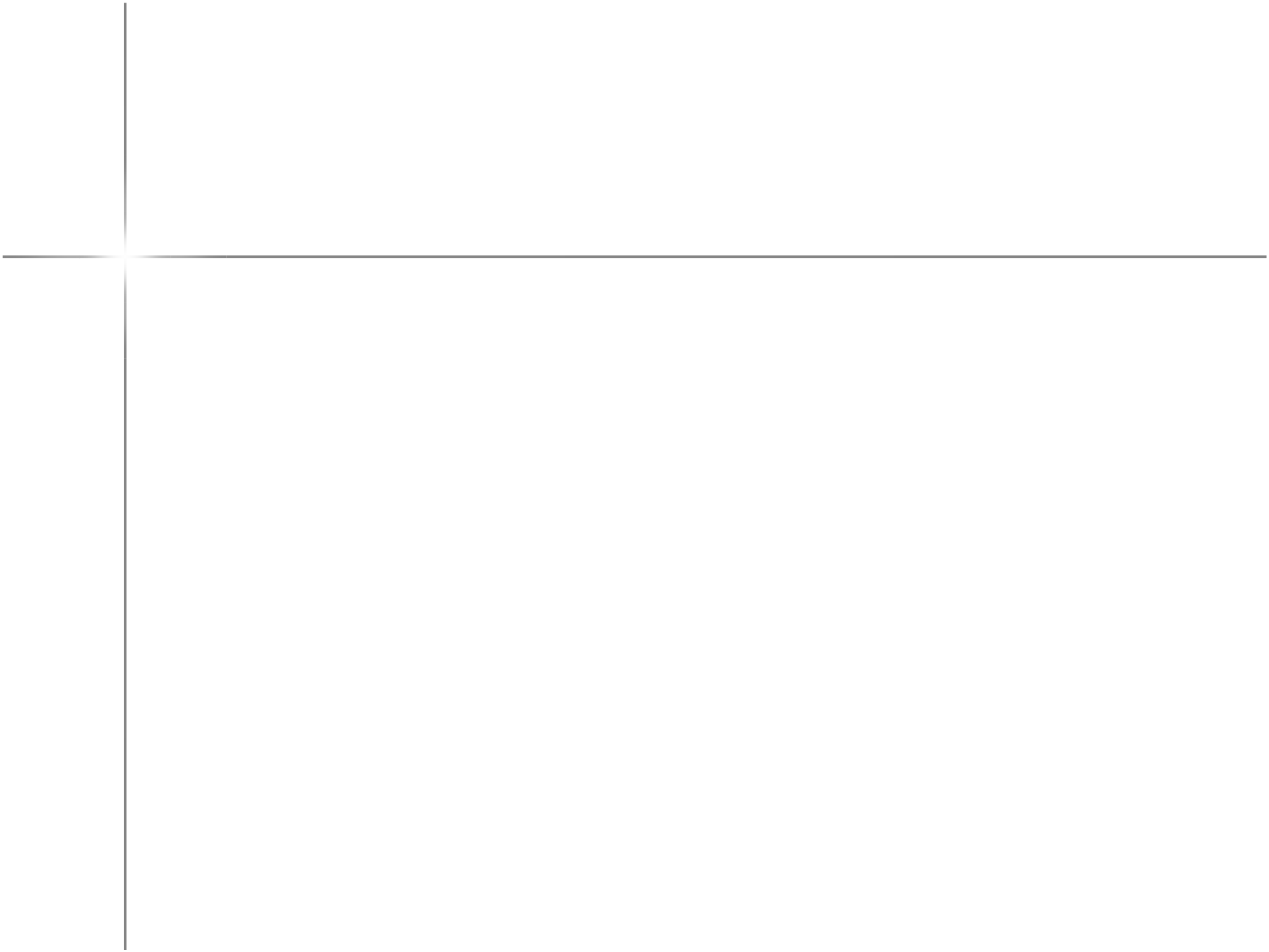
- Internal vs. External Scientific Validity
- What counts as enough background "evidence"
- Practical Uncertainty
  - Species variability
  - Growing conditions
  - Extraction methods
  - Extrapolation from limited data
  - Biologically active constituents
  - ? Dosing
  - Purity, quality, standardization.

Scientific Validity: Inclusion/Exclusion Criteria

- Ability to answer the scientific question
- Desire for generalizable knowledge

Scientific Validity: Outcome Measures

- Ability to answer the scientific question
- Desire for generalizable knowledge



Cultural Differences

- Culturally mediated risk tolerances
  - ? “acceptable” risk
- Societal vs. individual benefit
- Culture of adverse events reporting
- Prior beliefs about risk/benefit

Cultural Differences
Potential for Bias

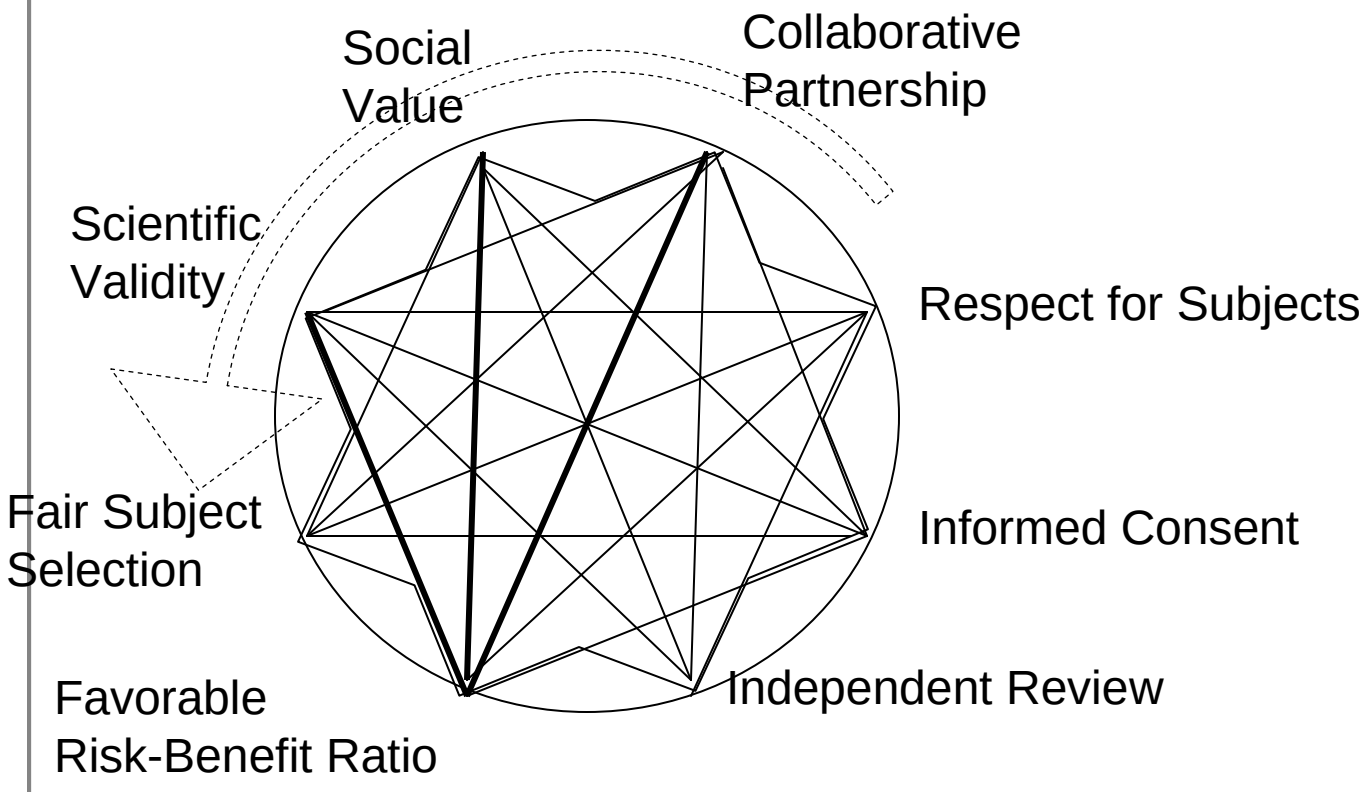
- Optimism Bias
- Pessimism Bias
- Precautionary Principle

Burden of Proof for Safety: Two Perspectives

?

Guilty until proven innocent	Innocent until proven guilty

8 Ethical Requirements



Asia Flower Case

- Social value depends on who you ask
- Scientific validity: considerable uncertainty
  - ? Historical Use
  - ? Pharmacodynamics/Pharmacokinetics
  - Mechanisms is likely unknown
  - Adverse events reporting insufficient
  - Generalizable vs. Rigorous scientific outcomes
- Favorable Risk Benefit Ratio:
  - Scientific uncertainty
  - Individual vs. societal benefit
  - Culturally determined risks tolerances

Case Summary

- Don’t Say “Yes”: NIH Investigators ought not to commit to a large treatment trial
- Don’t Say “No”: Consider negotiating with the partner country to conduct mechanistic studies, dose ranging studies and infrastructure for adverse events reporting.

Key Points

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BIOETHICS
AT THE NIH

CAM Research – Practical Strategies for Ethical Research

- Establish Shared Values/Vocabulary for risk/benefit determination
- Build relationships with content experts
- Evaluate the need for a longer-term commitment
- Agree on administrative procedures (Adverse Events)
- Negotiated Evidence Framework
  - Role of historical use
  - Standards for background research
    - Dosing
    - Standardization
    - Purity
- Research Policy: "Portfolio" Management – ought not treat projects in isolation to determine social value
  - efficacy research, mechanistic research, hypothesis generating vs. hypothesis testing

CAM Research – Ethical or Not?

1. Moxibustion for breach presentation
2. Hypnosis for cervical dysplasia
3. Decoction of XYZ1 for tamoxifen hot flashes
4. *Hypoxis* for HIV